USE OF TRIPROLIDINE IN PROVIDING REFRESHEDNESS ON WAKING

The invention relates to a novel use of a known compound, in particular to the use of that compound in the form of a consumable film in the treatment of sleep disorders experienced by a person, whatever the cause of those disorders

The present invention also relates to a method for the treatment or prevention of grogginess, drowsiness or lethargy on waking from sleep, to the use of triprolidine in the form of a consumable film as an aid to waking refreshed and to the use of triprolidine in the form of a consumable film as both a sleep aid and a means to wake refreshed thereafter.

Although much is known about the use of various pharmaceutical sleeping formulations as aids to sleeping, little has been published about the possibility of a sleep aid enabling an individual to wake refreshed as opposed to merely experiencing degrees of hangover effects such as grogginess, drowsiness, lethargy, etc.

Many people experience, either on an occasional or chronic basis, difficulty in achieving a satisfactory amount of sleep. Such a problem may be attributable to external factors, such as factors causing stress or anxiety, to excessive use or misuse of stimulants (such as caffeine) or depressants (e.g. alcohol), or to temporary disturbance of the person's lifestyle, e.g. occasioned by shift-working or long-haul travel through different timezones. Difficulty in sleeping may also be caused by chronic pain, e.g. pain caused by sciatica etc. Whatever the cause, the condition may be generally considered to be a sleep disorder and may commonly be referred to as "insomnia". It may manifest as difficulty in falling asleep and/or wakefulness during the desired period of sleep, leading to a shortened duration of sleep and/or disruption of the normal pattern of sleep.

The result of these difficulties will commonly be fatigue during the period of wakefulness, which may itself lead to stress and exacerbate the problem.

Various products are available to assist a user in overcoming problems of the type described above. Such products, commonly called "sleeping pills" may, however, suffer from disadvantageous side-effects. For example, while the products may be effective in sending a user to sleep, their effect may be of short duration, resulting in premature wakening. In other cases, the user may achieve the desired length of sleep but may awake with feelings of grogginess (a "hangover" effect). Such products may also be addictive. Tolerance may also develop to the drug which results in a decrease in effectiveness.

In other circumstances, a person may not suffer from sleep disorders as such, but may simply wish to achieve a particularly good night's sleep. In other words, the use of such products may be elective, rather than necessitated by a clinical need.

In addition to this well documented problem, many people also experience difficulties on waking such as grogginess, lethargy and drowsiness; difficulty in becoming fully alert and an absence of feeling refreshed. These phenomena are not necessarily linked to the number of hours sleep or always encountered as a result of drugs taken prior to sleep such as alcohol, medication, etc. Furthermore, individuals encountering tiredness during waking hours and other individuals having difficulty with insomnia resort to sleep aids in an attempt to increase or improve sleeptime rest. Nevertheless, it is also well documented that a negative side effect of sleep aids can also be an increased feeling of grogginess on waking.

Triprolidine, (E)-2-[1-(4-methylphenyl-3-(1-pyrrolidinyl)-1-propenyl]pyridine, is a first generation anti-histamine and has been marketed alone and, in combination with pseudoephedrine (a decongestant), for the treatment of allergic rhinitis. Triprolidine is known to have sedative effects and has been shown to have an adverse effect on the cognitive functions of users. These are undesirable side-effects for an anti-histamine and may account for the limited extent to which triprolidine has been used in clinical practice. More recently-developed, second generation anti-histamines are less prone to such side effects, and most recent studies involving triprolidine have used that compound as a positive control against which the more modern anti-histamine compounds have been compared. Such studies have generally been conducted using healthy volunteers following day time dosing, rather than persons suffering from

any form of sleep disorder, and have been concerned with the effects of the drug on day-time performance.

One study is known to have investigated the effect of triprolidine (amongst other anti-histamines) on sleep directly (*Nicolson et al, Neuropharmacology (1985) 24, 3, 245-250*). In that study single doses of triprolidine (10mg or 20mg sustained release) were given at bedtime to volunteers. It was found that triprolidine did not significantly alter "sleep onset latency" (i.e. the time required to fall asleep) compared with placebo. It was also found that, compared with placebo, triprolidine had no effect on wakefulness during sleep or total sleep time.

It has now been found that, contrary to what might have been expected in the light of previous studies, triprolidine can be used for inducing, prolonging or enhancing sleep, and that its use is accompanied by important benefits in comparison with other compounds known for this purpose that could not have been predicted.

It has also been found that triprolidine surprisingly increases the level of refreshedness felt upon waking if taken before sleeping. Advantageously, this effect is observed whilst triprolidine also acts as a sleep aid in facilitating the onset of stage I sleep and whilst enhancing sleep.

The increased level of refreshedness felt upon waking after taking triprolidine prior to sleeping was not expected and there has been no known disclosure of such an effect previously encountered.

The use of consumable films is well known for delivery of drugs via both the buccal cavity and the digestive tract, WO 99/17753, WO 98/26780, WO 98/20862 and WO 98/26763. WO 00/18365 discloses physiologically acceptable films including a water soluble film-forming polymer such as pullulan and antimicrobially effective amounts of the essential oils thymol, methyl salicylate, eucalyptol and menthol. The films can also include pharmaceutically active agents. Triprolidine hydrochloride is disclosed as one such pharmaceutically active agent. Methods for producing such films are also disclosed.

According to a first aspect of the present invention there is provided the use of a consumable film comprising triprolidine or a salt or hydrate thereof as active ingredient of an aid to waking refreshed after sleeping.

According to a second aspect of the present invention there is provided the use of a consumable film comprising triprolidine or a salt or hydrate thereof as active ingredient in the preparation of a composition for enabling an individual to wake refreshed after sleeping.

According to a third aspect of the present invention there is provided the use of a consumable film comprising triprolidine or a salt or hydrate thereof as active ingredient in the preparation of a medicament for enabling an individual to wake refreshed after sleeping.

According to a fourth aspect of the present invention there is provided the use of a consumable film comprising triprolidine or a salt or hydrate thereof in the preparation of a sleep aid which also enables an individual to wake refreshed after sleeping.

According to a fifth aspect of the present invention there is provided the use of a consumable film comprising triprolidine or a salt or hydrate thereof as active ingredient of a sleep aid which also enables an individual to wake refreshed after sleeping.

According to a sixth aspect of the present invention there is provided the use of a consumable film comprising triprolidine or a salt or hydrate thereof as active ingredient in the preparation of a medicament for the treatment or prevention of a sleep disorder which also enables an individual to wake refreshed after sleeping.

According to a seventh aspect of the present invention there is provided a method for the treatment or prevention of grogginess, drowsiness or lethargy on waking from sleep in a mammal comprising the administration to the mammal in need thereof of a consumable film comprising a non-toxic effective dose of triprolidine or a salt or hydrate thereof prior to the desired sleeping time.

According to an eighth aspect of the present invention there is provided a method for enabling an individual to wake refreshed after sleeping comprising the administration to the individual in need thereof and prior to the desired sleeping time of a consumable film comprising a non-toxic effective dose of triprolidine or a salt or hydrate thereof.

According to a ninth aspect of the present invention there is provided a method for aiding an individual's sleep and for also enabling the individual to subsequently wake refreshed after sleeping comprising the administration to the individual in need thereof and prior to the desired sleeping time of a consumable film comprising a non-toxic effective dose of triprolidine or a salt or hydrate thereof.

According to a tenth aspect of the present invention there is provided a waking refreshed aid comprising a consumable film comprising triprolidine or a salt or hydrate thereof as active ingredient in association with a pharmaceutically acceptable carrier therefor and instructions for administration thereof at or just before the desired sleeping time.

According to an eleventh aspect of the present invention there is provided a pharmaceutical formulation for the treatment or prevention of grogginess, drowsiness or lethargy on waking after sleeping, in the form of a consumable film comprising triprolidine or a salt or hydrate thereof as active ingredient in association with a pharmaceutically acceptable carrier therefor and instructions for administration thereof at or just before the desired sleeping time.

According to a twelfth aspect of the present invention there is provided a pharmaceutical formulation for enabling an individual to wake more refreshed after sleeping, in the form of a consumable film comprising triprolidine or a salt or hydrate thereof as active ingredient in association with a pharmaceutically acceptable carrier therefor and instructions for administration thereof at or just before the desired sleeping time.

According to a thirteenth aspect of the present invention there is provided a method of treating sleep of a person suffering from a sleep disorder, which method comprises

administration of a consumable film comprising an effective dose of triprolidine as active ingredient to such a person.

According to a fourteenth aspect of the present invention, there is provided the use of a consumable film comprising triprolidine as active ingredient in the manufacture of a composition for the treatment of sleep disorders.

According to a fifteenth aspect of the invention, there is provided a method for inducing, prolonging and/or enhancing sleep, which method comprises administration of a consumable film comprising an effective dose of triprolidine as active ingredient to a person desirous of achieving sleep.

In a related aspect of the invention, there is provided the use of triprolidine as active ingredient in the manufacture of a consumable film composition for inducing, prolonging and/or enhancing sleep.

It will also be understood that the term "inducing, prolonging and/or enhancing sleep" may encompass the treatment of a sleep disorder, i.e. a difficulty in achieving satisfactory sleep due to some internal or external factor, e.g. pain, stress or anxiety, misuse of stimulants or depressants, or temporary disturbance of lifestyle. Alternatively, it may encompass elective desires on the part of a user to achieve a particularly beneficial period of sleep. Such a desire may, for instance, arise in anticipation of important events the following day for which a person may wish to be fully alert and refreshed. In any event, the term "sleep disorder" as used herein should be taken to independently include any one or more of the foregoing and, specifically, any objective or subjective difficulty in an individual in any one or more of the following:-

- getting to sleep, especially stage 1 sleep
- staying asleep
- sleeping well
- waking refreshed
- waking alert
- keeping awake
- keeping alert

- keeping refreshed
- performing well the next day

The present invention also extends to the use of triprolidine as a sleep aid. By definition, a sleep aid extends to use by a healthy individual who elects for a sleep aid, for example, before an important event. The term "sleep aid" as used herein includes any one or more of the following benefits:-

- faster onset to stage 1 sleep
- increasing duration of sleep periods
- decreasing the number and duration of awakenings
- increasing total duration of sleep
- increasing probability of sleeping well
- improving insomnia, especially chronic or mild-moderate insomnia
- decreasing disturbances during sleeptime
- improving quality of sleep,
- as determined by any standard or known subjective or objective measures, for instance the Karolinska scale, Loughborough sleep log or actimetry.

The method of aiding an individual's sleep typically indicates aiding in the sense of providing any one or more of the above mentioned benefits.

Typically, the percentage of individuals who, after taking a dose of triprolidine before sleeptime, wake refreshed after sleeping is in the range 1-100%, more typically, 5-70%, most typically 10-35%. An especially typical range as aforesaid is 15-30% or even more especially 20-30%. Typically, by the terms "waking refreshed" or "wake refreshed" is meant that an individual felt at least refreshed on waking, preferably, the terms are defined as the individual felt very refreshed or refreshed in accordance with the Loughborough sleep log.

Typically, the percentage of individuals who, after taking a dose of triprolidine before sleeptime, wake refreshed after sleeping is more than 2%, more typically, more than 8% and most typically, more than 15%. An especially typical level as aforesaid is more than 18% or even more especially more than 20%.

By the term sleeping as referred to herein is meant an individual in at least Stage I sleep. By the term sleeptime as referred to herein is meant the time an individual desires to go to sleep.

Typically, the percentage of individuals who, after taking a dose of triprolidine before sleeptime, felt alert after sleeping is in the range 1-100%, more typically, 5-60%, most typically 10-30%. An especially typical range as aforesaid is 15-30% or even more especially 20-30%.

Typically, the percentage of individuals who, after taking a dose of triprolidine before sleeptime, felt alert after sleeping is more than 2%, more typically, more than 8%, most typically more than 12%. An especially typical level as aforesaid is more than 16%.

By the term felt alert is meant that an individual felt at least alert on waking. Preferably, the term is defined as the individual felt alert, very alert or extremely alert in accordance with the Karolinska 9-point scale.

Typically, the percentage of individuals who, after taking a dose of triprolidine before sleeptime, felt sleepy on waking is less than 25%, more typically, less than 20%, most typically less than 15%. An especially typical level as aforesaid is less than 14% or even more especially a mean level of less than 12%.

By the term felt sleepy is meant that an individual felt sleepy on waking. Preferably, the term is defined as the individual felt sleepy or very sleepy in accordance with points 8 or 9 of the Karolinska 9-point scale.

Preferably, in use of the present invention as defined herein, the mean subjective feeling of refreshedness after waking as, for instance, determined on a 5 point scale, e.g.. by the morning log of the Loughborough sleep log, is increased by at least 2%, more typically, by at least 4%, most typically, by at least 5%, as compared with an equivalent dose of placebo.

Typically, in use of the present invention as defined herein, the mean subjective feeling of refreshedness after waking as for instance, determined on a 5 point scale,

e.g.. by the morning log of the Loughborough sleep log, is increased by between 1-20%, more typically, 1-15%, most typically 2-10% as compared with an equivalent dose of placebo.

The degree of refreshedness and quality of sleep may be determined by the "morning" log of the Loughborough sleep log with the highest degree of refreshedness or quality of sleep being represented as 1 and the lowest being represented as 5. Accordingly, the percentage increase in refreshedness or quality of sleep is measured in this context by the decrease in the mean refreshedness or quality of sleep.

Preferably, by the use of the present invention, the response of awakening very refreshed or refreshed, as determined, for instance, by the morning log of the Loughborough sleep log, is improved by at least 20 %, more preferably, by at least, 30%, most preferably by at least 40%, as compared with an equivalent dose of placebo.

Typically, by the use of the present invention, the response of awakening very refreshed or refreshed, as determined, for instance, in accordance with the morning log of the Loughborough sleep log is improved by between 5% and 100%, more typically, by between 10% and 80%, most typically by between 20% and 60%, especially 40-55% and more especially 40-45% as compared with an equivalent dose of placebo.

Preferably, by the use of the present invention, the response of feeling extremely alert, very alert or alert, as determined, for instance, in accordance with the Karolinska 9-point scale, is improved by at least 2%, more preferably, by at least, 5%, most preferably by at least 10%, as compared with an equivalent dose of placebo.

Typically, by the use of the present invention, the response of feeling extremely alert, very alert or alert, as determined, for instance, in accordance with the Karolinska 9 point scale, is improved by between 1% and 40%, more typically, by between 2% and 30%, most typically by between 10% and 20%, as compared with an equivalent dose of placebo. An especially preferred range is 10-30%.

Preferably, by the use of the present invention, the response of feeling sleepy and needing to make some effort to stay awake or very sleepy, as determined, for instance, in accordance with points 8 and 9 of the Karolinska 9 point scale, is improved (i.e. decreased) by at least 2%, more preferably, by at least, 4%, most preferably, by at least 10%, as compared with an equivalent dose of placebo.

Typically, by the use of the present invention, the response of feeling sleepy and needing to make some effort to stay awake or very sleepy, as determined, for instance, in accordance with points 8 and 9 of the Karolinska 9 point scale is improved (ie. decreased) by between 1% and 100%, more typically, by between 2% and 75%, most typically, by between 4% and 60%, as compared with an equivalent dose of placebo.

Preferably, in use of the present invention as defined herein, the sleeptime awakenings, as for example determined by the Night diary of the Loughborough sleep log, may be decreased by 2-40%, typically, by 10-35%, most typically by 15-30%, as compared with an equivalent dose of placebo. An especially preferred range is 15-40%. Preferably, in use of the present invention as defined herein, the sleeptime awakenings may be decreased by more than 5%, more preferably by more than 10%, most preferably, by more than 15%, as compared with an equivalent dose of placebo.

Preferably, in use of the present invention as defined herein, sleep disturbance index (SDI), as for instance determined by actimetry, may be decreased by more than 5%, more preferably by more than 10%, most preferably by more than 15% as compared with an equivalent dose of placebo.

Preferably, in use of the present invention as defined herein, SDI may be decreased by 5-30%, more typically 5-25%, most typically 10-20 % as compared with an equivalent dose of placebo. An especially preferred range is 10-30%, more especially 10-25%.

Preferably, in use of the present invention as defined herein, time to sleep onset (TTSO) as, for instance, determined by actimetry may be decreased by 5-40%, more typically 15-35%, most typically 20-30% as compared with an equivalent dose of placebo. An especially preferred range is 20-40%, more especially 20-35%.

Preferably, in use of the present invention as defined herein, the time to sleep onset (TTSO) as compared with an equivalent dose of placebo is decreased by at least 10%, more preferably by at least 15%, most preferably, by at least 20%.

Preferably, the quality of sleep experienced as felt after awakening is also improved by the use of the present invention, typically the quality of sleep is improved by 2-30%, more typically 5-30%, most typically 10-20% as compared with an equivalent dose of placebo and as, for instance, determined by the morning log of the Loughborough sleep log. Typically, in use of the present invention as defined herein, the quality of sleep is improved by at least 2%, more preferably at least 5%, most preferably at least 10% as compared with an equivalent dose of placebo.

Preferably, in use of the present invention, the time to fall asleep as determined, for instance, by the Night diary of the Loughborough sleep log is decreased by 1-40%, more typically 5-35%, most typically 10-30%. An especially preferred range is 10-40%, more especially 10-35%. Typically, in use of the present invention as defined here, the time to fall asleep as aforementioned is decreased by at least 2%, more typically, by at least 5%, most typically by at least 10% as compared with an equivalent dose of placebo.

Preferably, by the use of the present invention, the response of sleeping extremely well or very well , as determined, for instance, in accordance with the morning log of the Loughborough sleep log, is improved by at least 20%, more preferably, at least, 35%, most preferably at least 50%, as compared with an equivalent dose of placebo.

Preferably, by the use of the present invention, the response of sleeping extremely well or very well, as determined, for instance, in accordance with the morning log of the Loughborough sleep log, is found for at least 20% of individuals, more preferably, at least 25%, most preferably, at least 30%. For example over 35% of individuals had such a response.

Typically, by the use of the present invention, the response of sleeping extremely well or very well, as determined, for instance, in accordance with the morning log of the Loughborough sleep log is improved by between 10% and 200%, most typically, by

between 20% and 150%, more typically by between 25% and 135% as compared with an equivalent dose of placebo. Typically, by the use of the present invention, the response of sleeping extremely well or very well, as determined, for instance, in accordance with the morning log of the Loughborough sleep log is found for between 25% and 100% of individuals, more typically, 30-80% most typically 35-70%. Especially preferred is the response in at least between 35-60%, of individuals, more especially 35-45%.

It will be understood that references herein to "triprolidine" include the compound (E)-2-[1-(4-methylphenyl-3-(1-pyrrolidinyl)-1-propenyl]pyridine as well as salts thereof that are acceptable for administration to the human body. Acid addition salts may particularly be mentioned, including the hydrobromide and hydrochloride salts. The hydrochloride salt, i.e. triprolidine hydrochloride, is particularly preferred for use in accordance with the invention. Solvates of triprolidine, notably hydrates, e.g. monohydrates, and to the extent that triprolidine may exist in polymorphic forms, all such polymorphs are within the scope of the invention.

The term "refreshed" as used herein means an individual waking refreshed or alert after a dose of triprolidine has been administered prior to sleep. In this context, the determination of whether an individual is feeling "refreshed" may be made by a subjective test. An example subjective test is measuring the degree of alertness on, for instance, the Karolinska scale or the feeling of being refreshed as determined by, for instance, the Loughborough sleep log. Alternatively, refreshedness may be based upon the inverse relationship between refreshedness and relative levels of sleepiness as determined by the Karolinska scale.

By the term individual as referred to herein is meant any mammal or human.

The administration of the active ingredient in accordance with the invention may be beneficial in that there is evidence that users feel more refreshed upon awakening, which is not the case with other treatments for sleep disorders, or indeed in the absence of any treatment, and do not experience grogginess or a "hangover" effect after the required number of hours sleep. This too is surprising in view of the fact that such feelings have been reported in relation to other active ingredients which have a comparable mode of action to that of triprolidine. Furthermore, there is no evidence

that repeated use of the active ingredient over the course of several days leads to any loss of effect.

The administration of the active ingredient in accordance with the invention may also be beneficial in that it may decrease the time required for a user to fall asleep, which is surprising in view of the previously-reported studies on volunteers. In addition, the total period of sleep may be increased and the incidence and duration of night-time wakenings experienced by the user may be reduced.

The active ingredient may be co-administered, either simultaneously or sequentially, with another pharmacologically active agent, presently preferred formulations contain triprolidine as the sole active agent and also triprolidine in combination with a further pharmaceutically active agent.

The invention extends to a kit comprising a first pharmaceutically active dosage form having triprolidine as the active agent, a second pharmaceutically active dosage form and instructions on how to administer the said first and second dosage forms.

The said first and second dosage forms may be located in separate compartments of a pharmaceutical pack.

The said dosage forms may be combined into a combined dosage form for simultaneous administration.

Preferably, the said at least one further active pharmaceutical agent is intended to be used in the treatment of a condition having sleep disorder as a symptom or potential symptom.

The said further active pharmaceutical agent may include, without limitation, antacids, analgesics, anti-inflammatories, antibiotics, laxatives, anorexics, antivirals, antiasthmatics, antidiuretics, antiflatulents, antimigraine agents, antispasmodics, additional sedatives, antihyperactives, tranquilizers, antihistamines, decongestants, betablockers, antidepressives, hormones and combinations thereof.

More preferably, the further active pharmaceutical agent is an active agent for treatment of pain, allergic conditions, migraine, coughing, a cold, flu, viral infections, throat infection, stress.

Preferably, the said further active pharmaceutical agent is independently intended for use as a, or in the treatment of pain, allergic reactions, migraines, coughs, anaesthetics, antiviral agents, disinfectant, anxiety, decongestant or women's health (such as menopausal or period problems).

Preferably, the said at least one further active pharmaceutical agent is independently selected from: an active agent used in the treatment of pain relief, migraines, allergies, colds, flu, coughs, anxiety, or women's health; an active agent used as an anaesthetic, antiviral agent, decongestant or disinfectant.

More preferably, the active agent is selected from an active agent used in the treatment of pain relief, allergies, anxiety, migraines, colds, flu, coughs and as a decongestant or antiviral agent.

Most preferably, the active agent is selected from an agent used in the treatment of colds, coughs, pain relief and flu.

Preferably, the said at least one further active agent is independently selected from a group consisting of Ibuprofen, Fluribiprofen, Ketoprofen, aspirin, Paracetamol, Aceclofenac, Codeine, Naproxen, Indomethacin, Diclofenac, Cox II, Meloxicam, Nitric oxide, Caffeine, Acrivastine, Cetirizine, Loratadine, Fexofenadine, Terfenadine, Beclomethasone, Hydrocortisone, Triptans, Almotriptan, Rizatriptan, Naratriptan, Sumatriptan, Zolmatriptan, Domperidone, Acetylcysteine, Menthol, Ambroxol, Carbocisteine, Dextromethorphan, Guaiphenesin, Ipecacuanha, Phenylpropanolamine, Liquorice, Marshmallow, Squill, Honey, Glycerine, Aniseed, Benzocaine, Lidocaine, Amantadine, Aciclovir, Famciclovir, Ganciclovir, Rimantadine, Penciclovir, Tribavirin, Valaciclovir, Neuraminidase inhibitors, Zanamir, Oseltamir, Benzalkonium chloride, Cetylpyridinium chloride, Dichlorobenzyl alcohol (dcba), Amylmetacresol(amc), Dequalinium chloride, Hexylresorcinol, Eucalyptus oil, Thymol, Calamine, Propranalol, Chamomile, Hops, Passion flower, Valarian, Melatonin,

Eucalyptus, Phenylepherine, Pseudoephedrine, Cranberry and Bisphosphonates or a pharmaceutically acceptable salt of any of the foregoing.

A more preferred range of active agents is independently selected from a group consisting of Ibuprofen, Fluribiprofen, Cox II such as meloxicam, triptans, Domperidone, Ambroxol, Dextromethorphan, Guaiphenesin, Lidocaine, Amantadine, Hexylresorcinol, dcba, amc, Propranalol, pseudoephedrine and Bisphosphonates or a pharmaceutically acceptable salt of any of the foregoing.

Optionally, the further active pharmaceutical agent may be combined with triprolidine in a single dosage form or in a pharmaceutical pack containing at least two dosage forms, one being triprolidine and the other being the said further active pharmaceutical agent. Preferably, the said pack includes instructions on how to take and/or mix the combination of triprolidine with the said further active pharmaceutical agent.

Preferably, the dosage of the said further pharmaceutically active agent is one suitable for the treatment selected. Preferably, a single dosage form of said pharmaceutically active agent is in the range 0.1mg -2000mg, more preferably, 0.2mg -1000mg, most preferably, 0.5mg -1000mg.

Typically, the dosage form for a pharmaceutical active in the treatment of pain is in the range 1–2000 mg, more preferably, 5-1000 mg depending upon the suitable dose level of the further active pharmaceutical agent.

Typically, the dosage form for a pharmaceutical active in the form of triptans is in the range 0.1–200 mg, more preferably, 0.5-100 mg depending upon the suitable dose level of the further active pharmaceutical agent.

Typically, the dosage form for a pharmaceutical active in the treatment of viral infections is in the range 1–1000 mg, more preferably, 50-300 mg depending upon the suitable dose level of the further active pharmaceutical agent.

Typically, the dosage form for a pharmaceutical active in the treatment of allergies is in the range 0.1–500 mg, more preferably, 0.5-200 mg depending upon the suitable dose level of the further active pharmaceutical agent.

Typically, the dosage form for a pharmaceutical active in the treatment of coughs and colds is in the range 0.1–500 mg, more preferably, 1-200 mg depending upon the suitable dose level of the further active pharmaceutical agent.

Typically, the dosage form for a pharmaceutical active in the treatment of upper respiratory tract problems is in the range 0.1–100 mg, more preferably, 0.5-50 mg depending upon the suitable dose level of the further active pharmaceutical agent.

Typically, the dosage form for a pharmaceutical active in the treatment of anxiety is in the range 0.1–200 mg, more preferably, 1-100 mg depending upon the suitable dose level of the further active pharmaceutical agent.

The active ingredient is preferably formulated in such a manner as to lead to non-sustained, substantially immediate release of the active ingredient, i.e. the formulation is preferably free of ingredients intended or effective to prolong or sustain release of the active ingredient.

Administration of the active ingredient in accordance with the invention is by means of a consumable film. The films may be edible and upon disintegration, the triprolidine may be absorbed via the buccal cavity or the digestive tract. Preferably, the triprolidine is formulated to be absorbed via the digestive tract. Suitable formulations are disclosed in WO 00/18365, the content of which insofar as it relates to consumable film formulations which may incorporate triprolidine hydrochloride or methods of producing such formulations is incorporated herein by reference.

For formulation in the presently preferred form, the active ingredient will generally be combined with various excipients in a manner which is known *per se*.

Suitable excipients for consumable films are disclosed in WO 00/18365 and these are incorporated herein by reference.

Thus, according to a further aspect of the invention, there is provided a consumable film for enabling an individual to wake refreshed after sleeping, which film comprises triprolidine as sole active ingredient in admixture with one or more suitable excipients,

the film comprising more than 0.01mg and less than 4.9mg triprolidine and the film being substantially free from menthol, thymol, methyl salicylate and eucalyptol.

The consumable film is one adapted to adhere and dissolve in a mouth of a consumer and comprises at least one water soluble polymer. Preferably, the said water soluble polymer is selected from the group consisting of pellulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl polymer, amylose, high amylose starch, hydroxypropylated high amylose starch, dextrin, pectin, chitin, chitosan, levan, elsinan, collagen, gelatin, zein, gluten, soy protein isolate, whey protein isolate, casein and mixtures thereof.

Preferably, other excipients may be utilised and these may be selected from water, antimicrobial agents, additional film-forming agents, plasticizing agents, flavouring agents, sulphur precipitating agents, saliva stimulating agents, buffering agents, cooling agents, surfactants, stabilising agents, emulsifying agents, thickening agents, binding agents, colouring agents, sweeteners, fragrances and the like.

Saliva stimulating agents can also be added as excipients. Saliva stimulating agents include food acids such as citric, lactic, malic, succinic, ascorbic, adipic, fumaric and tartaric acids. Preferred food acids are citric, malic and ascorbic acids. The amount of saliva stimulating agents in the film is from about 0.01 to about 12 wt% , preferably about 1 wt% to about 10 wt%, even more preferably about 2.5 wt% to about 6 wt%.

Buffering agents include salts of the aforementioned acids such as alkali metal salts of the food acids detailed above. An especially preferred buffering agent is sodium citrate. The amount of buffering agent may be in accordance with that suitable to complement the saliva stimulating agent as detailed above but is typically 0.01 – 12 wt%.

Preferred plasticizing agents include triacetin in amounts ranging from about 0 to about 20wt%, preferably about 0 to 2 wt%. Other suitable plasticizing agents include monoacetin and diacetin.

Preferred cooling agents include monomethyl succinate, in amounts ranging from about 0.001 to 2.0 wt%, preferably about 0.2 to about 0.4 wt%. A monomethyl succinate containing cooling agent is available from Mane. Inc. Other suitable cooling agents include WS3, WS23, Ultracool II and the like.

Preferred surfactants include mono and diglycerides of fatty acids and polyoxyethylene sorbitol esters, such as, Atmos 300 and Polysorbate 80. The surfactant can be added in amounts ranging from about 0.5 to about 15 wt %, preferably about 1 to about 5 wt% of the film. Other suitable surfactants include pluronic acid, sodium lacryl sulphate, and the like.

Preferred stabilising agents include xanthan gum, locust bean gum and carrageenan, in amounts ranging from about 0 to about 10wt%, preferably about 0.1 to about 2wt% of the film. Other suitable stabilising agents include guar gum and the like.

Preferred emulsifying agents include triethanolamine stearate, quaternary ammonium compounds, acacia, gelatin, lecithin, bentonite, veegum and the like, in amounts ranging from about 0 to about 3wt%, preferably about 0.01 to about 0.7 wt% of the film.

Preferred thickening agents include methylcellulose, carboxyl methylcellulose, and the like, in amounts ranging from about 0 to about 20wt%, preferably about 0.01 to about 5 wt%.

Preferred binding agents include starch, in amounts ranging from about 0 to about 10wt%, preferably about 0.01 to about 2 wt% of the film.

Suitable sweeteners that can be included are those well known in the art and similarly, flavourings and colourings that can be included are those known in the art. A suitable definition of sweeteners, flavourings and colourings is found in WO 00/18365, page 12 line 17 – page 16 line 19, the contents of which are hereby incorporated herein by reference.

The amount of active ingredient to be administered in a single dose may vary quite widely, depending *inter alia* on the desired effect. However, a formulation will generally contain at least 0.01 and up to 20mg of active ingredient, more commonly at least 0.5mg and less than 10mg of active ingredient, most commonly no more than 5mg, e.g. 1.25 or 2.5mg. Doses of fast melt formulations would be expected to deliver the active ingredient more quickly and efficiently, may contain less active ingredient, e.g. between 0.1 and 1.0mg, e.g. about 0.5mg. Preferably, such formulations contain active ingredient in the range 0.01-2.5mg, more preferably, 0.05-1.0mg and most preferably, 0.1-0.5mg.

In general, the desired dose (which may comprise one or more unit doses, e.g. one or two films) will be taken by a user prior to the desired time at which it is desired for the composition to take effect. Most commonly, the dose will be taken at night-time, i.e. prior to the user sleeping through hours of darkness. Typically, the dose may thus be taken after 8pm in the evening or later, say after 9pm or after 10pm. Typically, it may be recommended that the user take the composition between 0.5 minutes and 2 hours and more commonly between 1 minute and 2 hours prior to the time at which he or she wishes to fall asleep. Most commonly, the composition may be taken about 10 to 30 minutes prior to that time. In addition, however, the active ingredient may be effective, particularly at lower doses, in restoring sleep, e.g. in the event of night-time waking.

Preferably, the use of triprolidine in any aspect of the invention as defined herein is its use as active ingredient. Preferably, the triprolidine in any aspect of the invention defined herein is in the form of a non-toxic effective dose, preferably, suitable for any given mammal or human and determined in accordance with age and weight.

Preferably, to obtain the benefits on waking or otherwise as defined herein, the active ingredient of triprolidine administered before sleeptime is less than 10mg, typically less than 5mg, more preferably, less than 4.5mg, most preferably less than 4.0mg. Especially preferred is a dose as aforesaid of less than 3.5mg and most especially preferred is a dose of less than 3.0mg. Typically, the dose of triprolidine is between 0.01 and 10.0mg, preferably, between 0.01 and 4.9mg, more preferably, between 0.1 and 4.5mg, most preferably between 0.5 and 4mg. Especially preferred is a dose of between 1 and 3.5mg and more especially a dose of between 2.0 and 3.0mg. Most

especially preferred is a dose as aforesaid of about 2.5mg or 1.25mg. Preferably, the above dosage levels are based on triprolidine hydrochloride monohydrate and amounts of other salts or hydrates should be varied accordingly to deliver the equivalent amount of active ingredient.

The consumable films of the present invention may be referred to as buccal wafers whether or not they are absorbed via the buccal cavity or the digestive tract.
In the buccal wafer formulations of the present invention, the triprolidine may be in any suitable release form such as a slow release, sustained release, immediate release or uncontrolled release form.

Preferably, the dose of the triprolidine in accordance with the invention may be taken by an individual before it is desired to go to sleep (sleeptime), preferably less than two hours before sleeptime, more preferably, less than one hour before sleeptime, most preferably, less than 20 minutes before sleeptime. Especially preferred is to take the dose of triprolidine less than 15 minutes before sleeptime.

Preferably, the dose of triprolidine is less than 4 doses per day (24 hour period), more preferably, less than 3 doses per day, most preferably less than 2 doses per day. Especially, preferred is 1 dose per day.

The packaging of the invention as defined herein may be in any suitable form such as, for example, a film dispenser etc. The packaging of the invention may be associated with instructions for any of the features or preferred features of the invention as defined herein.

For the avoidance of doubt, reference to the "use of the present invention" herein should be taken to include "the method of the invention", and "use of a pharmaceutical formulation" as well as use of the present invention per se.

Advantageously, the use of triprolidine in the present invention results in a reduced hangover or morning grogginess effect as compared with other sleep aids or sleep disorder remedies. More advantageously, the use of triprolidine in the present invention provides an improved degree of refreshedness or more refreshed feeling

upon waking as determined by the Loughborough sleep log or Karolinska scale and as compared with placebo.

For the avoidance of doubt, reference to quantities of triprolidine herein should be taken as references to quantities of the hydrochloride mono hydrate (HCl. H_2O) form. However, it should be appreciated that the invention extends to other forms, including all pharmaceutically active salts and hydrates thereof.

The term refreshed as used herein may be substituted by any term selected from alert, invigorated, revitalised, re-energised, recharged, rejuvenated, attentive, awake or words having the like effect or equivalent general meaning and the term refreshedness may also be substituted by the grammatical equivalent thereof from the words aforesaid. In addition, the term alert as used herein can be substituted by any of the above alternative terms.

Examples of formulations which may be used in the invention are as follows:

Example 1

Example 1 was produced in accordance with the following composition and constituted the trial formulation unless otherwise mentioned hereinafter. Patients received one tablet for the 2.5mg dose and two tablets for the 5.0mg dose.

Name of Ingredient		mg/tablet
1.	Triprolidine HCl. H_2O	2.5
2.	Micro-crystalline Cellulose	29.0
3.	Lactose H_2O	60.0
4.	Magnesium Stearate	1.0
5.	Croscarmellose Sodium	10.0

Method

(a) Triprolidine hydrochloride (1) was mixed with approximately one-half of the components (2)-(5) and thoroughly mixed. The remainder of components (2)-

(5) were added and mixing continued to achieve uniform distribution of the active ingredient in the mixture.

(b) The mixture was compressed to form tablets, each containing 2.5mg of active ingredient, in a tablet forming machine.

Example 2

Formulation of Buccal Wafer

	%w/w
Xantham Gum	0.2
Hydroxypropylmethylcellulose	46
Carrageenan	2
Purified water	37.8
Citric acid	5
Triprolidine Hydrochloride	5
Sodium citrate	5
Flavour	0.5
Colour	0.5

Method of Manufacture

Mix the following excipients together to form a suspension.Disperse the HPMC in water until homogenous. Add the Xanthan gum and carraggenan to the mix. Mix triprolidine hydrochloride in water. Mix the triprolidine with the gum mixture and add the citric acid and sodium citrate followed by the colours and flavours.

Coat the suspension onto a processing foil and dry using a multistage drying process

Once dry cut into individual wafers of approximately 50 mg and package accordingly.

Clinical Trial

The efficacy of triprolidine in enabling a patient to feel refreshed or alert upon waking after taking triprolidine prior to sleeptime was investigated using patients with a history of sleep disorders and utilising triprolidine prepared in accordance with example 1.

The study herein utilised the following determination methods:-

(a) Karolinska scale as defined in: Int. J. Neuroscience 52 29-37 (1990); and
- validation: Sleep 17 (3) 236-41 (1994)

(b) Loughborough Sleep log as defined in : Sleep 17 (2) 146-159 (1994); and
Sleep 18 (2) 127-134 (1995)

(c) Actimetry – AW4 actimeters (Cambridge Neurotechnology) were worn continuously throughout the study. A button was pressed at night when the subject desired to go to sleep and again in the morning upon waking. The results of the actimeter study were analysed in the manner defined by Horne et al (Sleep, 17(2); 146-159).

SDI% was calculated as follows:-

$$SDI = \frac{\text{Number of 30 second epochs with movement}}{\text{Number of 30 second epochs from total time spent in bed}} \times 100$$

This is the measure of:

1. The length of time it took to fall asleep
2. Any awakenings throughout the sleep period

Expressed as a % of total time spent in bed.

Study Objectives

- To evaluate the effects of two doses of triprolidine compared with placebo.

Study Design

A multiple-dose, placebo-controlled, parallel-group, double-blind, randomised study investigating the effects of 2.5mg and 5mg triprolidine in patients with temporary sleep disturbance.

Male and Female candidates aged 18 years and above were recruited to one of five research centres by means of local advertising. Candidates were screened by means of a telephone questionnaire and selected candidates invited for interview at the research centre. Key inclusion criteria used to select candidates for the study were:

- A record of poor sleep at least 2 nights per week
- A record of poor sleep for at least 1 week but not more than 3 months
- Sleep disturbance not caused by underlying disease
- No excess use of alcohol or drugs
- Sleep disturbance affected daytime functioning

The candidates came to the research centre on Thursday or Friday and were fitted with a wrist actimeter (AW4 from Cambridge Technology) to establish a baseline measure for SDI and were provided with diary cards to record subjective assessments for the Loughborough Sleep Log and the Karolinska Sleepiness Scale. They returned to the investigational site on the Monday and were issued with the study compositions (2.5mg triprolidine, 5mg triprolidine or placebo). The investigator telephoned a central randomisation centre where the subject was randomised to a particular treatment group using a dynamic balanced randomisation algorithm. The subject was given three doses of their allocated study medication and instructed to take a single dose of two tablets 20 minutes before they intended to go to sleep on three consecutive evenings, commencing that evening. The diary cards for the Loughborough Sleep Log and Karolinska Sleepiness Scale were asked to be completed on waking.

The candidates returned to the research centre on the following Friday.

Parameters Evaluated

Candidates were required to complete a questionnaire 15 minutes after awaking on the feeling of refreshedness assessed on a 5-point scale, the Loughborough sleep log.

A daytime sleepiness assessment was also made 20 minutes, 2 hours and 4 hours after awaking on the Karolinska 9-point scale, i.e. the sleepiness scale.

Results

198 candidates completed the study, of whom 178 provided valuable data. (61 placebo, 60 on 2.5mg triprolidine and 57 on 5mg triprolidine. The subjects on 2.5mg dose took one tablet and placebo those on 5mg dose took 2x2.5mg tablets. The subjects on placebo took a dose to match the active treatments (2 tablets).

Key results were as follows:

- There was evidence that there was a lack of daytime sleepiness associated with those patients who took either dose of triprolidine
- The SDI was reduced for both treatments as compared with placebo on every treatment night
- The sleep latency onset was reduced for both treatments as compared with placebo on every treatment night

The following results were obtained for patients taking 2.5mg triprolidine. For the mean of the 3 nights:

- 15 minutes after waking, patients taking triprolidine recorded feeling more refreshed than those on placebo, as determined by the Loughborough sleep log($p < 0.05$).
- There were a greater percentage of people on 2.5mg triprolidine who, on waking were feeling alert, very alert or extremely alert than those on placebo as measured by the Karolinska log.

- There was a lower percentage of people on 2.5mg triprolidine who, on waking were feeling sleepy, and needing to make some effort or very sleepy, needing to make a great effort to keep awake than those on placebo as measured by the Karolinska log.
- There was no evidence of residual hangover effects / morning grogginess from the drug.
- The SDI was significantly reduced compared to those on placebo ($p<0.01$).
- The sleep latency onset was reduced as compared to those on placebo ($p<0.05$).

Further analyses show the advantageous effects of triprolidine in relation to the degree of refreshedness on waking.

The study design used 3 groups. On average, the number of individuals in each of the 3 groups (placebo, 2.5mg triprolidine and 5mg triprolidine) was 60 ± 10 patients.

In the trial, patients were tested during a seven day period and the results have been analysed for a mean of three days in the middle of this period. The effects of triprolidine at dose level 2.5mg and 5.0mg are compared with placebo in table 1.

Table 1

Datasets (a) to (g) – Main Analyses

		Placebo	2.5mg	5mg
(a) SDI (%)		Mean	Mean	Mean
(Sleep latency onset and	Mon	13.19	11.33	11.72
Quality of sleep)	Tues	14.58	12.15	12.71
(Actimeter)	Wed	14.46	11.2	11.81
	Mean of 3	14.26	11.56	12.23
(b)TTSO (min)		Mean	Mean	Mean
(Time to Sleep onset)	Mon	20.75	16.22	16.16
(Actimeter)	Tues	22.29	15.62	17.88
	Wed	20.26	14.8	16.36
	Mean of 3	22.16	15.53	16.93
(c) 15mins after awaking		Mean	Mean	Mean
(1- very refreshed	Mon	3.41	3.33	3.72
5- very tired)	Tues	3.46	3.23	3.56
(Loughborough sleep log)	Wed	3.42	3.18	3.54
	Mean of 3	3.45	3.24	3.59
(d) last night I slept		Mean	Mean	Mean
1- extremely well,	Mon	3.2	2.67	2.49

		Placebo	2.5mg	5mg
5- extremely badly)	Tues	3.06	2.71	2.93
(Loughborough sleep log)	Wed	3.02	2.81	2.64
	Mean of 3	3.11	2.73	2.69
(e) time to fall asleep (min)		Mean	Mean	Mean
(Loughborough sleep log)	Mon	33.61	23.67	22.02
	Tues	29.73	24.44	32.08
	Wed	28.35	20.95	24.24
	Mean of 3	30.98	23.93	26.5
(f) no of times woke up		Mean	Mean	Mean
(Loughborough sleep log)	Mon	1.9	1.18	1.49
	Tues	1.61	1.37	1.42
	Wed	1.43	1.11	1.39
	Mean of 3	1.71	1.22	1.42

Statistical Analysis

Generally the treatment groups were well balanced in terms of the demographic data. Unless otherwise mentioned all group data was analysed using ANOVA. In two cases, namely, how the patient felt 15 minutes after awakening in the Loughborough Sleep Log and the Karolinska Sleepiness Scale at 20 minutes, the two variables were analysed using ANCOVA by including the weekend and the mean of Friday/Saturday/Sunday night as a covariate. The method was a closed test procedure (Williams' test). Each of the tests were to be conducted at the 5% level. The analysis of the secondary endpoints was similarly conducted using the Student's t-tests on parameter estimates taken from the analysis of variance model presented above.

The following is a copy of the "Loughborough sleep log questionnaire" which was used by patients in the study and provided the data for datasets a and b in table 1.

"Loughborough Sleep Log" Questionnaire

This will be completed 15 minutes after waking.

Bedtime Log

I went to bed at : ..... I turned out the lights at : .....

The windows are : shut .....

Not shut .....

Morning Log

I woke up at ..... this morning I got out of bed at ..... this morning

15 minutes after waking I felt :		Last night I slept :	
a) very refreshed		a) extremely well	
b) refreshed		b) very well	
c) neither refreshed nor tired		c) fairly well	
d) tired		d) rather badly	
e) very tired		e) extremely badly	

Night Diary

During the night the windows were left : opened .....

shut .....

During the night the secondary glazing was left : opened .....

shut .....

During the night my partner slept in : the same bed as me .....

a different bed to me .....

As far as I can remember, it took me ..... minutes to fall asleep last night

As far as I can remember, I woke up ..... times last night

Please note the details of any awakenings you can remember in the table below.

Time Length of time awake (mins) Reason for awakening."

Table 2 shows additional data in connection with data set (a) showing the improvement in refreshed responses at the 2.5mg dosage of triprolidine hydrochloride monohydrate.

Table 2

Loughborough Sleep Log: Awoke Very Refreshed or Refreshed Responses

Day of Testing	*Monday*		*Tuesday*		*Wednesday*	
Dose	N	%	n	%	n	%
Placebo	10	15.2	10	16.4	11	18.3
2.5mg TRP.HCl.H_2O	14	23	14	23	16	25.8
5mg TRP.HCl.H_2O	7	11.5	5	8.2	9	14.8

Similarly, table 3 shows corresponding additional data in connection with data set (b).

Table 3

Loughborough Sleep Log: Last Night I Slept Extremely Well or Very Well Responses

Day of Testing	*Monday*		*Tuesday*		*Wednesday*	
Dose	N	%	n	%	n	%
Placebo	11	18	12	22.2	13	24.1
2.5mg TRP.HCl.H_2O	24	41.4	23	41.8	22	37.9
5mg TRP.HCl.H_2O	30	50.9	17	28.8	24	39.3

Karolinska's sleepiness scale is set out below and the results for placebo, 2.5 and 5.0mg doses of triprolidine are shown in tables 4 and 5. Table 4 relates to the number of individuals experiencing scales 1, 2 or 3 on the Karolinska scale and table 5 relates to the number of individuals experiencing scales 8 and 9.

Karolinska Sleepiness Scale

This will be completed 20 minutes after awakening and then at 2 hours and 4 hours following the first assessment on days 5, 6, 7 and 8.

1. Extremely alert
2. Very alert
3. Alert
4. Rather alert
5. Neither sleepy or alert
6. Some signs of sleepiness
7. Sleepy but no effort to keep awake
8. Sleepy, some effort to keep awake
9. Very sleepy, Great effort to stay awake, fighting sleep

Table 4

Karolinska 9-point scale

(a) I feel extremely alert, very alert or alert

Day of Testing	*Monday*		*Tuesday*		*Wednesday*	
Dose	n	%	n	%	n	%
Placebo	9	13.6	14	23.0	11	17.2
2.5mg TRP.HCl.H_2O	13	21.3	13	21.3	13	21.0
5mg TRP.HCl.H_2O	4	6.3	6	9.5	11	17.5

Table 5

(b) I feel (i) sleepy, [and need to make] some effort or (ii) very sleepy, a great effort to keep awake

Day of Testing	*Monday*		*Tuesday*		*Wednesday*	
Dose	n	%	n	%	n	%
Placebo	8	12.1	10	16.4	9	14.1
2.5mg TRP.HCl.H_2O	7	11.5	8	13.1	4	6.5
5mg TRP.HCl.H_2O	8	12.5	11	17.5	8	12.7

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The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive.

Each feature disclosed in this specification (including any accompanying claims, abstract and drawings), may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features.

The invention is not restricted to the details of the foregoing embodiment(s). The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.